MICHAEL P. WALLS
VICE PRESIDENT
REGULATORY & TECHNICAL AFFAIRS

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Dr. Barbara Shane
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NTP Office of Liaison, Policy and Review
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Re: Comments on 12th Report on Carcinogens (RoC)

Dear Dr. Shane,

The American Chemistry Council is pleased to respond to the National Toxicology Program's (NTP's) request for comments on the Report on Carcinogens (Federal Register / Vol. 73, No. 246 / Monday, December 22, 2008 / Notices 78364). The American Chemistry Council[1] (ACC) and its member companies have played an active role in screening and testing chemical substances, developing risk assessments and implementing science-based risk management policies. ACC supports NTP's research and testing efforts, and in particular encourages the use of more mechanistic data in hazard and risk assessments.

The NTP's Reports on Carcinogens (RoCs) are both nationally and globally significant documents in the area of chemical assessment. ACC was an active participant in the stakeholder comment process undertaken by NTP to strengthen the scientific quality and public participation processes in the development of the RoCs. On April 16, 2007, NTP published its revised final process for evaluation of candidate substances for the 12th RoC. These new processes include (1) public peer review of draft background documents by ad hoc scientific expert panels, (2) public peer review of draft substance profiles by the NTP Board of Scientific Counselors, and 3) preparation by NTP of a response to public comments made on the 12th RoC.

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $664 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.

While ACC strongly supports these improvements, we are concerned that NTP has not implemented these improvements in a manner that fully supports opportunities for substantive scientific dialogue among the most qualified chemical-specific and subject matter experts during the most critical stages of the RoC process. There are two areas where we believe NTP should consider immediate actions to address critical process shortcomings:

1. The Need for Independent Peer Review of Data Re-Analyses

Apparently, in the case of styrene, NTP is intending to rely on a re-analysis and/or re-interpretation of scientific study results which differ significantly from the conclusions of the original investigators. While ACC recognizes that it is important and entirely appropriate for the NTP Expert Panel and the NTP to comprehensively evaluate the whole of the scientific literature relevant to the listing criteria of the RoC, using a weight of the evidence process, there are concerns when a re-analysis or re-interpretation of published data are not subjected to the same rigorous and thorough analysis as the original work. These concerns are especially heightened when the conclusions reached by NTP differ from those of the authors of the original studies. At a minimum, in cases where re-analyses, meta-analyses or re-interpretations are conducted by NTP and the results differ substantially from the original studies, then NTP should not rely on such until 1) the results have been subjected to independent peer review and 2) stakeholders are provided sufficient opportunity to review the results and comment upon these to NTP. In addition, in certain circumstances, such as when the results of a re-analysis are greatly different from those of a study author, NTP should consider inviting the original study author to comment upon the NTP's re-analyses. Such a comment should be considered by NTP and made part of the public record. The perspectives of original authors and NTP's re-interpretations must be wholly transparent in NTP's documentation.

2. Addressing Critical Scientific Issues Raised in Public Comments

It is extremely important that NTP adhere to both the spirit and letter of the new processes that have been implemented in the RoC development to assure meaningful and substantive scientific dialogue. ACC is concerned that NTP's approach to responding to public comments falls short. By waiting to prepare any response to public comments until the last step (publication of the RoC and issuance by the Secretary of Health and Human Services to the public and to Congress), NTP is not demonstrating a commitment to engage in a scientific dialogue throughout all of the steps of the RoC development. By only responding to comments at the conclusion of the process, reviewers engaged at the different steps of the RoC development process cannot ascertain whether NTP considered comments provided by stakeholders during the early, most meaningful, phases of NTP's development of a substance's assessment. In ACC's view, a commitment to scientific dialogue requires more than simply accepting comments on an assessment. We suggest that in addition, NTP should develop a summary of comments at each critical stage of the RoC process and provide responses. Comments dealing with similar issues may be grouped, so that NTP does not need to list each and every comment. However, NTP should indicate a response to the most significant issues raised and describe NTP's perspective and rationale and, when appropriate, indicate how and where in the next iteration of the assessment, the information provided by the comment has resulted or will result in a change. Meaningful and substantive scientific dialogue requires that NTP commit to fully and openly addressing comments during the formative stages of the RoC and provide transparent and scientifically justified responses to the most significant issues raised.

ACC recognizes that addressing these two RoC process issues in a timely manner that does not unduly delay assessments may be challenging for the NTP. However, due to the importance of the RoC report, ACC requests that NTP consider approaches that can immediately and effectively address these RoC process shortcomings. Options NTP could consider include re-drafting of the draft substance profile and/or developing a response to the most significant comments received to date.

In addition to these process issues, ACC believes that there is a need for NTP to improve its approach for evaluating genotoxicity studies. There is a pressing need for NTP to adopt a formal, comprehensive and systematic approach for conducting a weight of evidence evaluation of genotoxicity studies. Studies can have positive or non-positive outcomes – that is, they support or do not support findings of an adverse effect for a particular substance and they can be of different quality – that is, they can be conducted under standard Good Laboratory Practices or peer-reviewed, or they can lack these quality assurances. Employing a formal weight of evidence evaluation is the most reasonable approach to informed evaluation and decision-making. In an objective manner, a weight of evidence evaluation considers the adequacy, strength, and consistency of the each study, and in turn, the overall data set. Positive studies do not inherently deserve greater weight; higher quality studies, positive or negative, do. Where there is a lack of concordance in the overall data set, decisions should be based on the preponderance of available data; in certain cases, development of additional new data may be beneficial to resolve conflicting information. A weight of evidence approach should include at least three basic components:

1. A data collection step during which available studies are searched for in the published literature and other sources, with the goal of ensuring that the breadth of reasonably available information is gathered for a particular decision.

2. A data evaluation step that considers the following issues: 1) The data relevance, 2) The data quality (including the extent of peer review), and 3) The data significance (the "weight" it deserves).

3. An integration step in which all of the data and their associated "weights" are brought together to develop an overall understanding of what is known, and the degree of confidence in this knowledge, with respect to the potential of a substance to be genotoxic.

Attached is an evaluation prepared by Cantox Health Sciences International (Cantox) of the genotoxicty data of styrene (Attachment 1). Based on their comprehensive review and analysis, Cantox concludes that in the evaluation of genotoxicity presented by NTP in the Draft Substance Profile (DSP), "there is an inherent bias to the presentation of "positive" results (i.e., to support a genotoxic effect) without any "weighing" of the results in light of their relevance to assessing the potential human carcinogenicity of styrene" and "the genetic toxicity data available on styrene cannot be extrapolated so as to suggest that they indicate a genetic, and therefore, carcinogenic risk, for styrene-exposed human populations."

Thank you for the opportunity to comment on the 12th RoC process.

Sincerely,

Vice President
Regulatory and Technical Affairs

Attachment 1: Comments on the Assessment of the Genotoxicity of Styrene Presented in the Draft Substance Profile Prepared For Potential Listing Of Styrene in the 12th Roc Prepared By Cantox Health Sciences International (Cantox)